Clinical Case Report

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Alveolar architectures preserved in cancer tissues may be potential pitfalls for diagnosis and histological subtyping of lung cancer

Three case reports

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Abstract

Rationale: Lung cancer is a leading cause of cancer-related deaths globally. Appropriate histopathological diagnosis and subtyping form the basis and are critical for clinical therapies.

Patient concerns: Here, we report about 3 patients who had a nodule in the lung. Cancer cells grow in the alveolar cavity in many lung carcinomas. In all our 3 cases preserved alveolar architectures were found in tumor tissues which may lead to diagnostic pitfalls.

Diagnoses: Three patients had tumors that were diagnosed as nonsmall cell lung cancers, including large-cell carcinoma, peripheral squamous cell carcinoma, and large-cell neuroendocrine carcinoma, all of which contained structures of preserved alveolar cells that could be mistaken as malignant glandular components. The preserved alveolar cells formed acinar or duct-like structures enwrapped in the lung cancer tissues or surrounded the nests of cancer cells. Proliferative alveolar cells adjacent to cancer tissues were observed, and papillary structures and marked atypia, both of which may be mistaken as part of adenocarcinoma or carcinoma with glandular differentiation, were also observed.

Interventions: All patients underwent surgery and postoperative chemotherapy.

Outcomes: The patients had no recurrence at 5-, 8-, or 10-month follow-up after the last surgery.

Lessons: Preserved alveolar cells with different architectures may be observed in various lung cancer tissues and may be mistaken as adenocarcinoma or carcinoma with glandular differentiation. Distinct morphological and immunohistochemical features may help distinguish preserved alveolar cells from tumor components.

Abbreviations: HE = hematoxylin and eosin, WHO = World Health Organization.

Keywords: adenocarcinoma, alveolar architecture, case series, large cell carcinoma, large cell neuroendocrine carcinoma, lung cancer

1. Introduction

According to the World Health Organization classification of lung, pleura, thymus, and heart, 4th edition, the percentage of adenocarcinoma has increased in recent years, especially in women.[1,2] There are different chemotherapy protocols for different types of nonsmall cell lung cancers, including adenocarcinoma, and the other histological types of lung cancer. Moreover, molecular-targeted treatments based on gene mutation, which are currently widely accepted, require clear and appropriate diagnosis and subtyping of lung cancer because of the different gene profiles of adenocarcinoma and other lung cancers.[3,4] Therefore, differentiating between adenocarcinomas and other types of lung cancer is important. Here, we report about 3 cases of lung cancer that may have been misdiagnosed as adenocarcinomas or carcinomas with glandular differentiation, including salivary gland tumors such as mucoepidermoid carcinoma and adenoid cystic carcinoma, with preserved alveolar architectures that may be mistaken as malignant glandular components. The absence of both cellular and histological atypia of preserved alveolar architectures and the distinct immunohistochemical features may help in differentiating these benign cells from malignant glandular structures.

2. Case reports

2.1. Case 1

A 57-year-old man presented with a tumor measuring approximately 3 cm in size and located in the peripheral part of the right lung. The cancer cells were large, arranged in nests, and had no obvious differentiation (Fig. 1A). The cancer nests were surrounded by a layer of cells, which were small and had no

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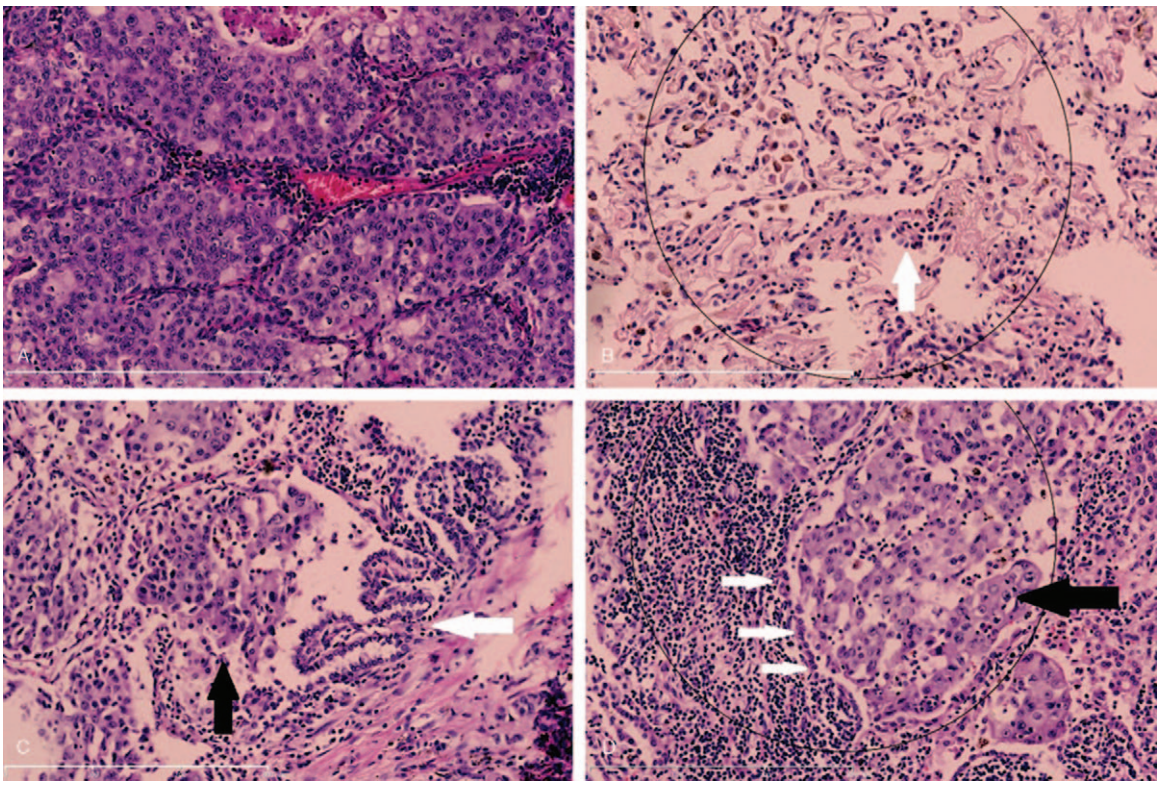

Figure 1. Histological features of the tumor of case 1. The cancer cells were large, arranged in nests, and had no obvious differentiation (A). The cancer nests were surrounded by a layer of small cells without obvious atypia. Proliferative alveolar epithelial cells were observed adjacent to cancer tissues (B, white arrow). Some of the alveolar epithelial cells formed papillary structures (C, white arrow). There were some cancer cells growing in the alveolar cavity, in which a little space remained (C, D, white arrows showing the preserved alveolar cells).

obvious atypia. Proliferative alveolar epithelial cells in the lung tissues adjacent to the cancer nests were observed (Fig. 1B). Some proliferative alveolar epithelial cells showed papillary structures (Fig. 1C), which could be easily mistaken as adenocarcinomas. Some cancer cells growing in the alveolar cavity, with a little space remaining, were also observed (Fig. 1D), indicating that the small cells surrounding the solid cancer cell nest were also alveolar epithelia. Immunohistochemical analysis results (Fig. 2) revealed that the cancer cells were negative for TTF-1, whereas the surrounding small cells without obvious atypia were positive for TTF-1. The immunostaining pattern of Napsin-A was consistent with that of TTF-1, which was positive in cancer nests but negative in the small surrounding alveolar cells. Staining for P40 and CD56 were negative in cancer cells. According to the immunostaining phenotype, the tumor was diagnosed as large-cell carcinoma, whereas the peripheral small cells were the alveolar epithelium rather than malignant glandular components. The patient underwent surgery and postoperative chemotherapy and had no recurrence at the 5-month follow-up after the last surgery.

2.2. Case 2

A 68-year-old woman presented with a tumor measuring approximately 5 cm in size and located in the peripheral part of the upper lobe of the left lung. The cancer cells were arranged in nests and showed squamous cell differentiation (Fig. 3A). Many round or irregular gland-like or tubular structures were observed in the cancer cell nests (Fig. 3A and B), which were also observed along the edges and outside of the cancer nests (Fig. 3C). The cells of these structures were small, showing no obvious atypia. Alveolar epithelial hyperplasia was found in the peripheral lung tissue of the tumor (Fig. 3D). A few cancer cells invaded the alveolar wall. The morphology of the alveolar epithelial cells was consistent with that of the gland-like or tubular structures in the cancer tissues. Immunostaining results (Fig. 4) showed that the cancer cells were positive for P63 but negative for TTF-1 and Napsin-A, whereas the small cells forming the gland-like or tubular structures in the cancer tissues were positive for both TTF-1 and Napsin-A. The Ki67 index was higher in cancer cells (approximately 50%) than in the small cells (<10%). According to these findings, this case was diagnosed as peripheral squamous cell carcinoma. The gland-like or tubular structures were preserved alveolar cells, which could be easily mistaken as malignant components, leading to a misdiagnosis of adenocarcinoma, adenosquamous cell carcinoma, or tumors of salivary glands such as mucoepidermoid carcinoma. The patient underwent surgery and postoperative chemotherapy and had no recurrence at the 8-month follow-up after the last surgery.

2.3. Case 3

A 75-year-old man presented with a tumor measuring approximately 4 cm in size and located in the left lung. The cancer cells were dense and arranged in nests (Fig. 5A), whereas the interstitial tissues were few. Many small gland-like cavities (Fig. 5B) or crack-like structures (Fig. 5C) were observed inside the cancer nests. These structures had a layer of small cells without obvious atypia (Fig. 5D). Because the cancer cells were very dense and the intensive gland-like structures were small, the coating cells were not easily observed and were more likely to be

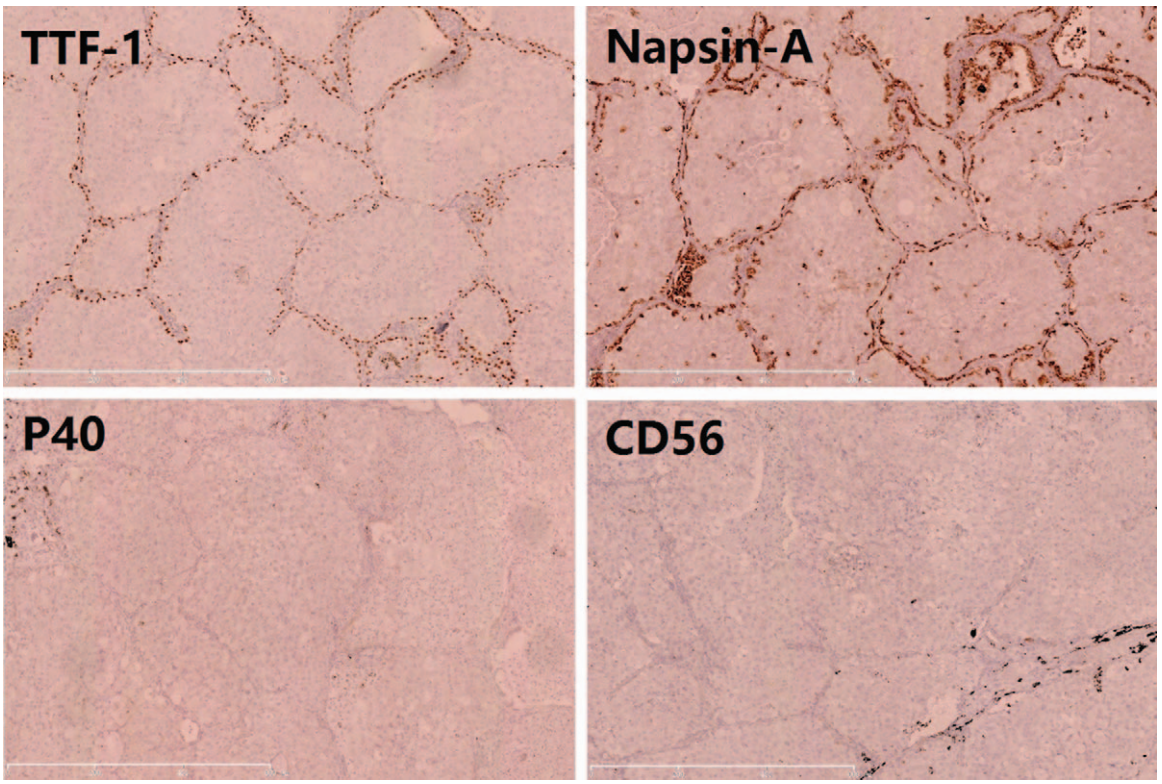

Figure 2. Immunohistochemistry of the case 1. The cancer cells were negative for TTF-1, Napsin A, P40, and CD56. The alveolar cells surrounding the cancer cell nests were positive for TTF-1 and Napsin-A.

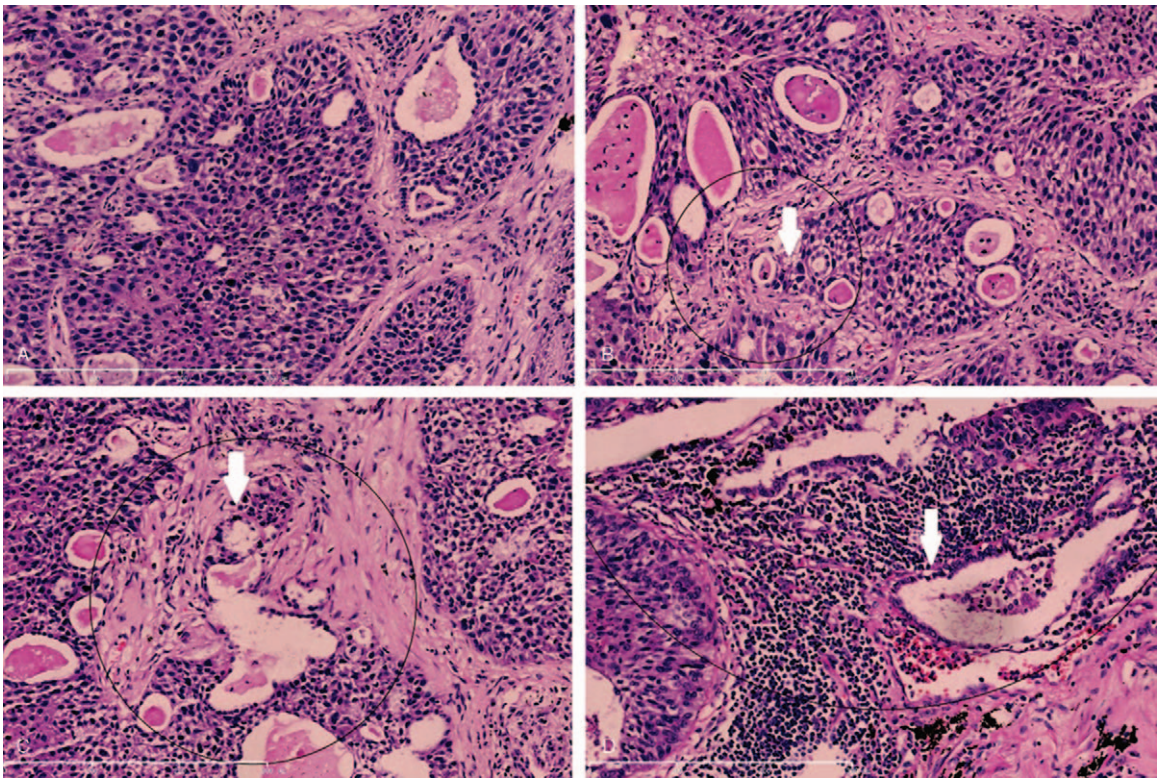

Figure 3. Histological features of the tumor of case 2. The cancer cells were arranged in nests and showed squamous cell differentiation (A). There were many round or irregular gland-like or tubular structures in the cancer cell nests (A, B), which were also observed along the edges and outside of the cancer nests (C). The alveolar epithelial hyperplasia was found adjacent to the cancer tissues (D, white arrows). A few cancer cells invaded the alveolar wall (D, black arrows).

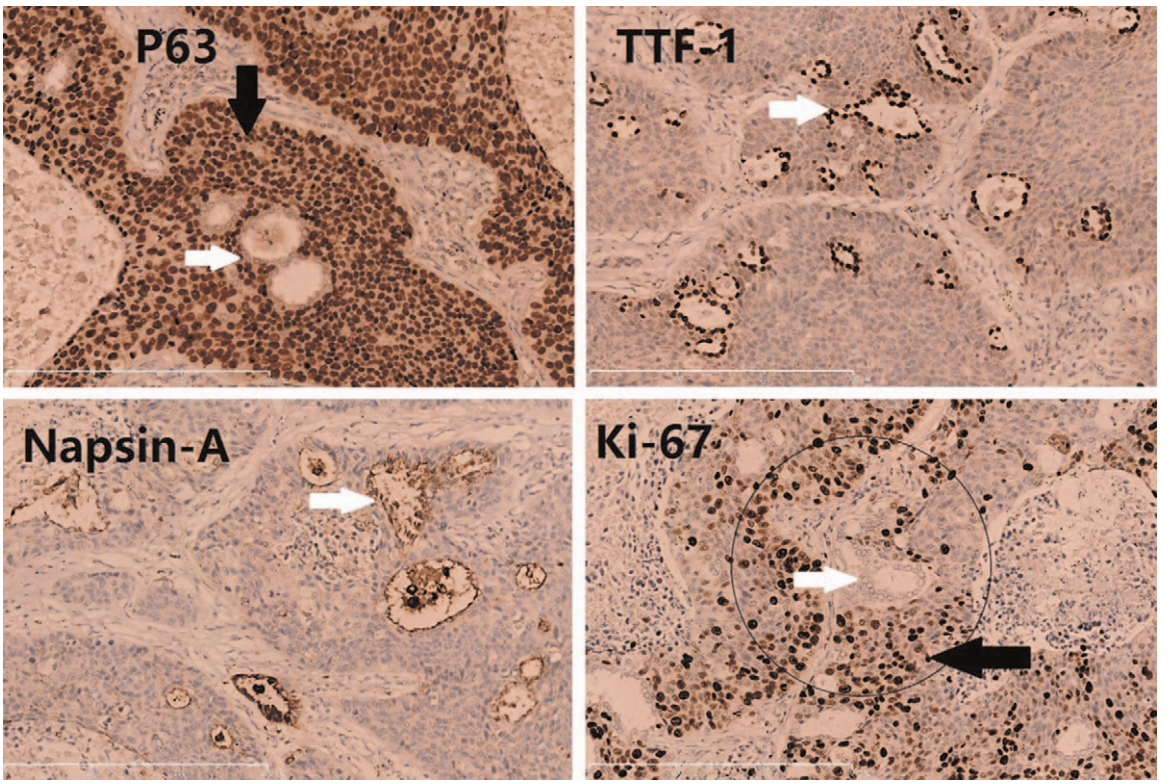

Figure 4. Immunohistochemistry of the case 2. The cancer cells were positive for p63, but the glandular like alveolar cells were negative for p63 (white arrow). The alveolar cells were positive for TTF-1 and Napsin-A (the white arrow). The Ki-67 index was high in the cancer nest but very low in the glandular architecture of alveolar cells (white arrow).

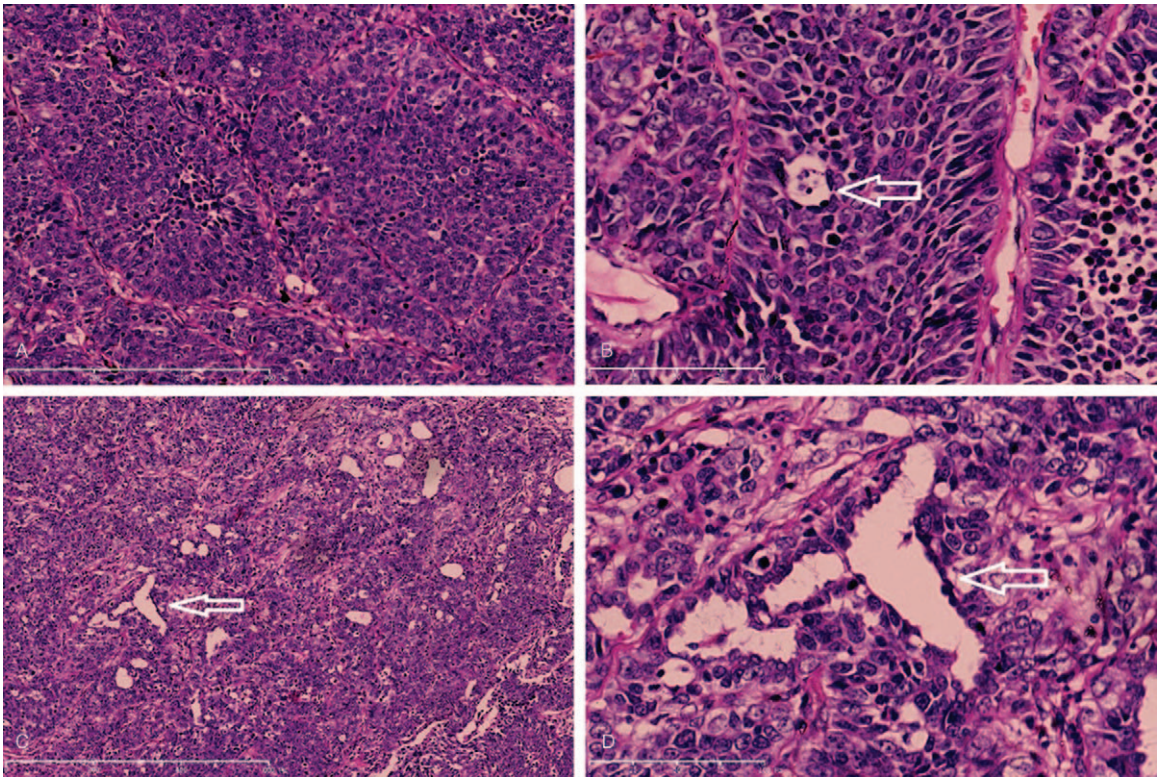

Figure 5. Histological features of the tumor of case 3. The cancer cells were dense and arranged in nests (A). Interstitial tissues were few. There were many small gland-like cavities (B) or crack-like structures (C) inside the cancer nests. These structures had a layer of small cells without obvious atypia (D).

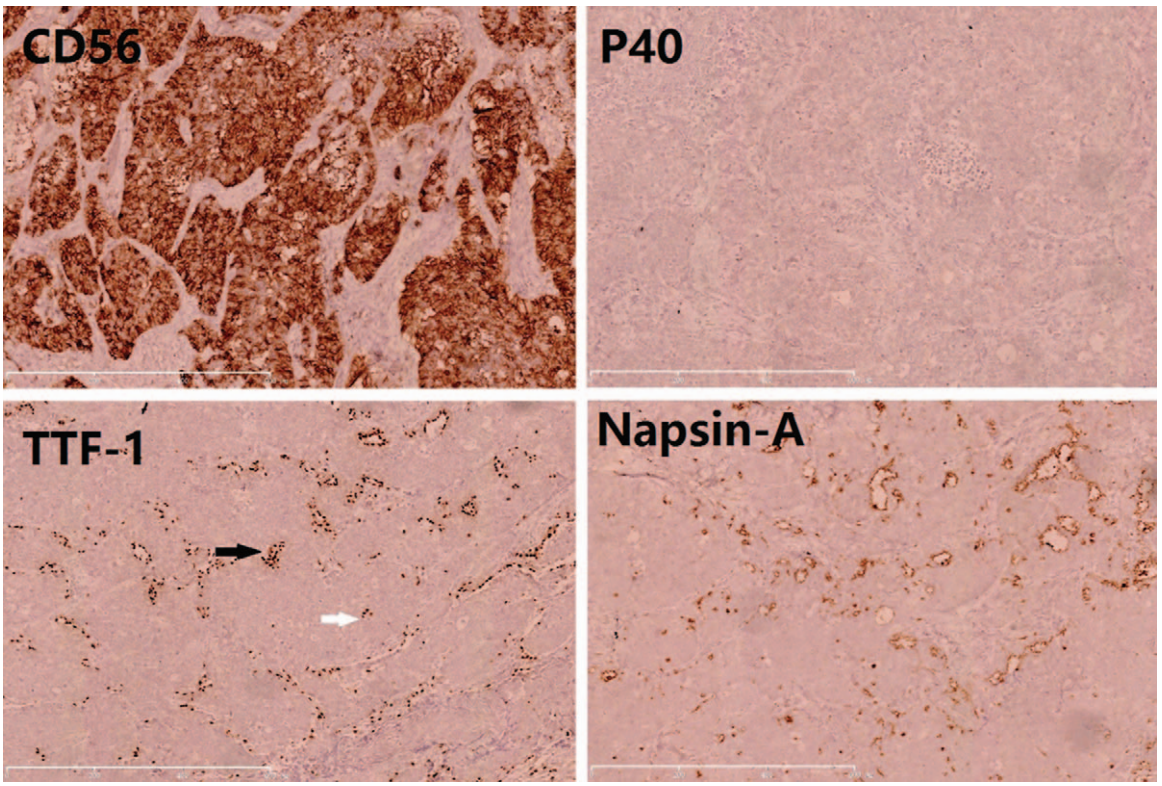

Figure 6. Immunohistochemistry of the case 3. The cancer cells were positive for CD56 but negative for p63, Napsin-A, and TTF-1. The cells of the gland-like structures were negative for p63, (white arrow) but positive for TTF-1 and Napsin-A (arrows).

mistaken for malignant components. Immunohistochemical analysis results (Fig. 6) revealed that the cancer cells were positive for CD56 but negative for P40, TTF-1, and Napsin-A. In contrast, the small cells forming gland-like structures were positive for TTF-1 and Napsin-A but negative for CD56. According to these results, this case was diagnosed as large-cell neuroendocrine carcinoma, and the gland-like structures were preserved alveolar cells but not malignant glandular components. The patient underwent surgery and postoperative chemotherapy and had no recurrence at the 10-month follow-up after the last surgery.

The tumors were pathologically examined via hematoxylin and eosin (HE) and immunohistochemical staining as described previously.[5] Written informed consent was obtained from the patients for publication of this case report. This report was approved by the institutional ethics committees of China Medical University and was conducted according to the ethical guidelines of the Declaration of Helsinki.

3. Discussion

Here, we report about 3 patients who had nodules in the lung that were diagnosed as large-cell carcinoma, peripheral squamous cell carcinoma, and large-cell neuroendocrine carcinoma based on distinct morphological and immunohistochemical features.

The proportion of various histological types of lung carcinoma has considerably changed since 2004.[1,2] Furthermore, therapies for lung cancer have considerably improved in recent years.[3,4] Molecular-targeted treatments have become important clinical treatment modalities for patients with lung cancer.[3,4] As gene profiles of lung carcinoma vary greatly depending on the histological subtypes, clear and appropriate diagnosis and subtyping are currently highly important for treating patients with lung cancer.

Our 3 cases of nonsmall cell lung cancer and nonadenocarcinomas were carefully differentiated from adenocarcinomas and carcinomas with components of glandular differentiation. These cases had preserved alveolar cells, which could lead to the consideration of adenocarcinomas or carcinomas with glandular differentiation. These cases were diagnosed as squamous cell carcinoma, large-cell neuroendocrine carcinoma, and large-cell carcinoma without specific differentiation. The tumor cells had various architectures of preserved alveolar cells. Moreover, proliferative alveolar cells were observed adjacent to the cancer tissues and had moderate atypia or even papillary structures. These proliferative alveolar cells could be important clues for preserved alveolar cells in cancer tissues. In case 1, the preserved alveolar cells were present around nests of cancer cells. The cells were positive for TTF-1 and could be mistaken as components of the carcinoma tissues, thus leading to the consideration of adenocarcinoma or carcinoma with glandular differentiation. Alveolar cells were also observed in the peripheral tissues, whereas the alveolar cavity was partially embedded in cancer cells. In many lung carcinomas, cancer cells grow in the alveolar cavity and gradually fill up the cavity.[6–8] However, the alveolar cells are preserved. Thus, alveolar cells, which are positive for TTF-1, are frequently observed around the cancer cell nests. Case 2 was diagnosed as peripheral squamous cell carcinoma that originated and was growing from the peripheral parts of the lung, which generally has specific histological features.[7–11] There were numerous cysts in and outside the cancer cell nests, which were positive for TTF-1 and thus could be mistaken as malignant granular components. The cyst or glad-like architectures inside

the cancer cell nest could particularly lead to the consideration of adenocarcinoma or carcinoma with glandular differentiation, such as tumors of salivary glands, for example, mucoepidermoid carcinoma or adenoid cystic carcinoma. Case 3 was diagnosed as large-cell endocrine carcinoma, which also had preserved alveolar architectures in the cancer tissues. In this case, the cancer cells showed marked dysplasia and the embedder epithelial cells were relatively small, irregular, and dispersed. Thus, the epithelial cells were more likely to be mistaken as malignant glandular components. However, when the cyst or crack-like architectures were carefully observed, the cells of these structures were noted to be very small with no marked atypia, indicating that they were preserved alveolar epithelial cells but not malignant components. The alveolar cells are frequently trapped in carcinoma tissues of the lung.[6] There were several clues for not mistaking these preserved alveolar cells as malignant glandular components. One was that the cells were small and identical and showed no marked atypia. Second was that the structures of the preserved alveolar cells were not connected with cancer cell nests, and there was no transition or connection between these 2 components. The preserved alveolar cells were randomly dispersed inside or outside the cancer nests. The third was that the preserved alveolar cells showed a very low Ki-67 index compared with cancer cells. The fourth was that proliferative alveolar cells were frequently observed in the peripheral region of cancer tissues, and the cancer cells could also be found in the alveolar cavity. These cells were consistent with preserved cells in the cancer tissues, and the structures could provide clues that TTF-1-positive small cells without marked atypia were preserved alveolar epithelial cells but not malignant glandular components.

Our cases demonstrate that lung cancers of various histological types show preserved alveolar structures in the cancer tissues, which is rarely mentioned in the current literature. The architectures include cyst or crack-like structures inside or outside cancer cell nests and epithelial cells surrounding the cancer cell nests. Several clues, including histological features and immunostaining findings, may help in differentiating these architectures from malignant glandular components. We suggest that avoiding misdiagnosis of preserved alveolar structures, especially those with dysplasia, as tumor components is essential for proper lung cancer subtyping and appropriate clinical treatment. However, the number of our cases is limited. Future investigation and analysis of a large sample will help in better understanding the oncogenesis, development, and clinicopathological features of lung cancer.

Author contributions

Conceptualization: Xiaoxi Fan, Xiupeng Zhang, Enhua Wang, Chuifeng Fan.
Formal analysis: Xiupeng Zhang.
Investigation: Xiupeng Zhang.
Supervision: Chuifeng Fan.
Writing – original draft: Xiaoxi Fan, Xiupeng Zhang.
Writing – review & editing: Enhua Wang, Chuifeng Fan.
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